

HELLER EHRMAN WHITE & MCAULIFFE LLP Sheet 1 of 8

Title: METHODS FOR THE PRODUCTION OF MULTIMERIC PROTEINS, AND RELATED COMPOSITIONS

Docket No.: 38814-351B, Gijs van Rooijen Filed: December 19, 2001

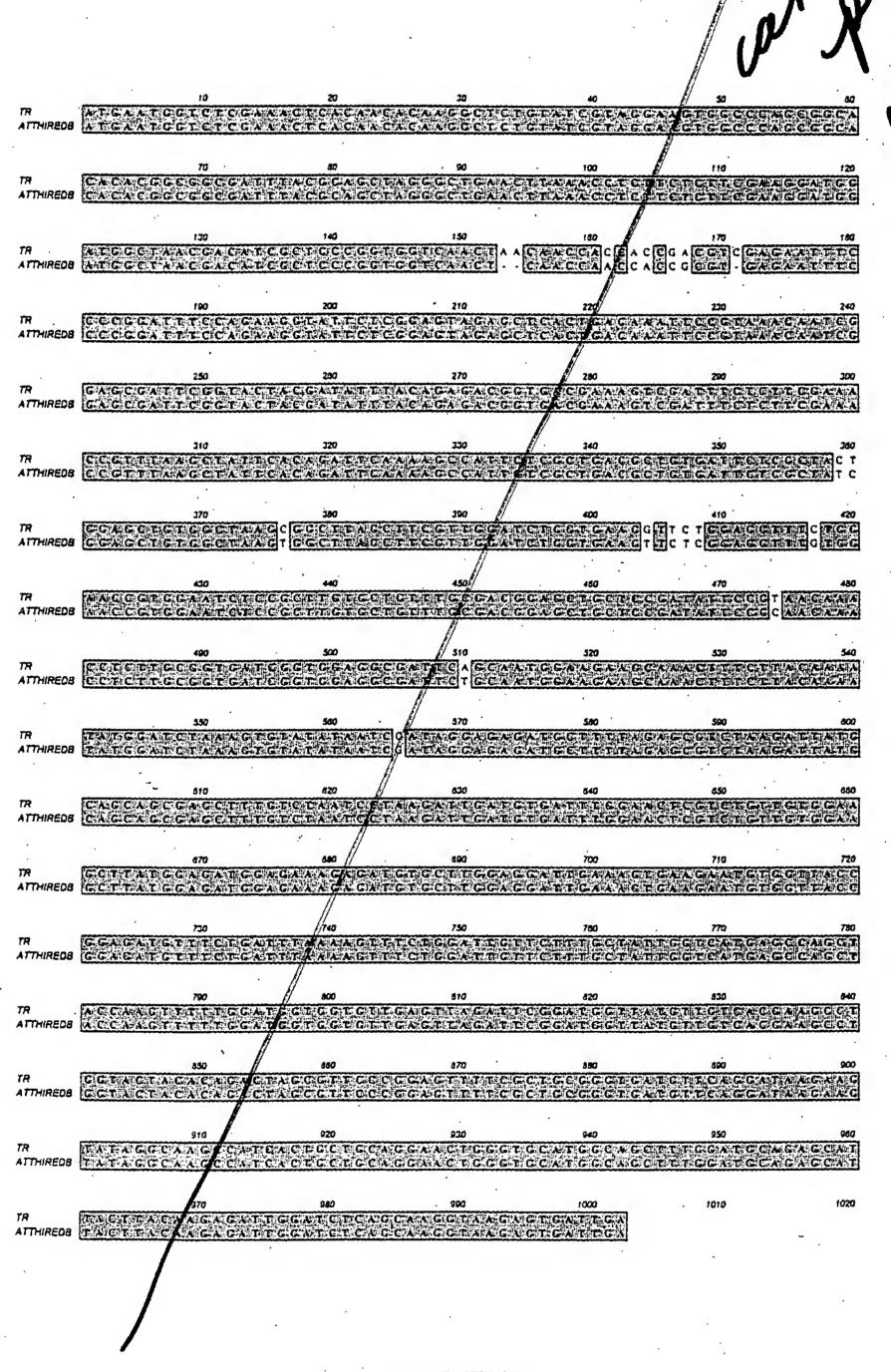


FIGURE 1





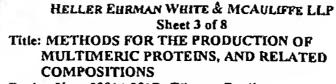


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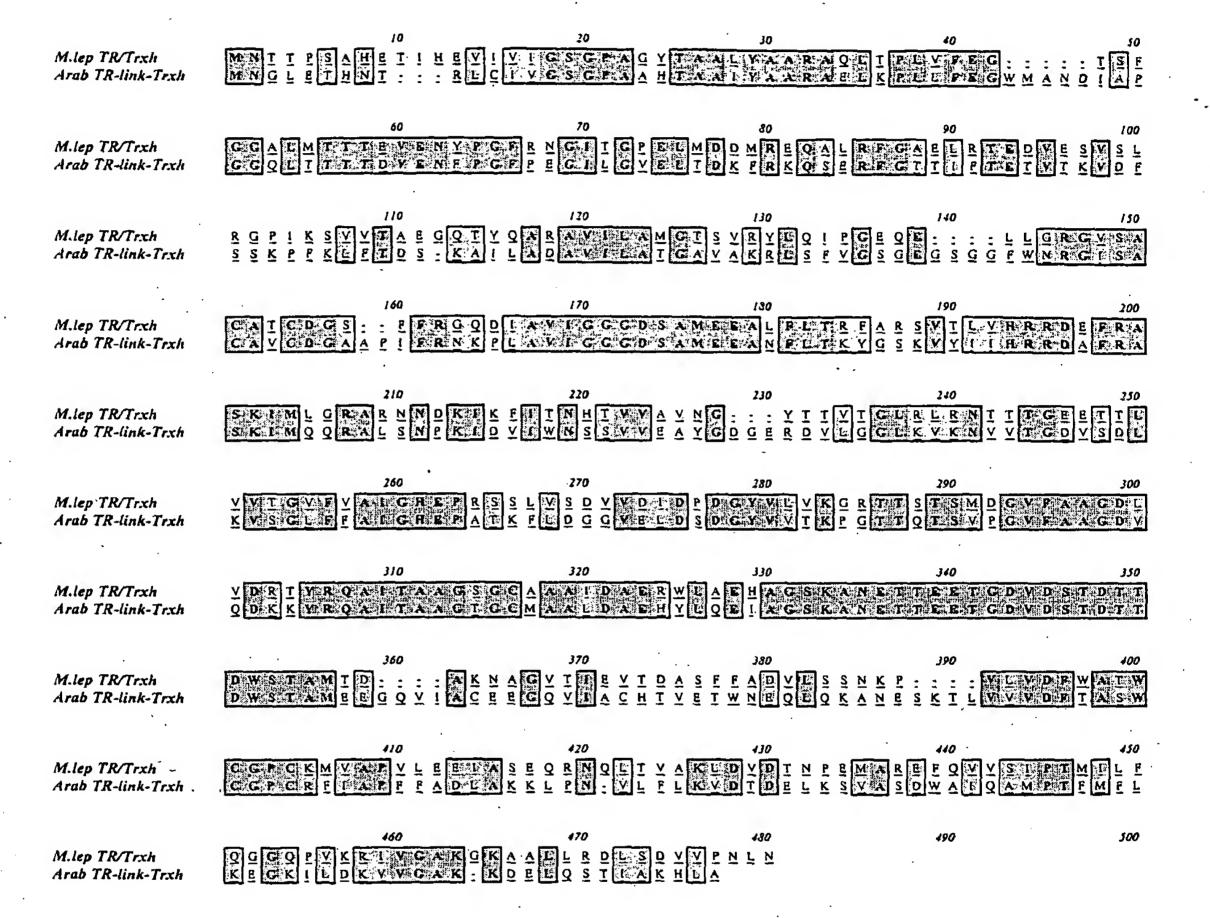
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		10	20	30	40	50	60
Translation of ATTHIRED8 Translation of TR	MNGLETH MNGLETH	NTERLICIEVICS C NERLICIEVICS C	PARHTARIYAA	RAELKTULPE RAELKTULPE	GWMAND LAFG	GOLTTTTDVE	
		70	80	90	100	110 -	120
Translation of ATTHIREDS Translation of TR	PGPPEGE	LGVELTDKPR	KQSERFGTTIF KQSERFGTTIF	TETVIKVORS TETVIKVDFS	SKPPKLPTDS	KALEADAVIL	Ž,
		130	140	150	160	170	180
Translation of ATTHIREDS Translation of TR		S.F.V.G.S.G.EVLG S.F.V.G.S.G.EG	GLWNRGTSACA GFWNRGISACA	SY CID G APA P F FF	HNK > LAVING GG	DSAMERAN PL	TK
		190	200	210	220	230	240
Translation of ATTHIREOS Translation of TR	YGSKVYI	I DRRDAFRAS	KIMQQRALSNI	KIDWIWNSS	VEAY GOGERD	VILOGIEKYKNY	V-T
		250	260	270	250	290	300
Translation of ATTHIRED8' Translation of TR	GDVSDLK GDVSDLK	V.S.G.L.P.A.L.G.H.	EPATKPEDGG EPATKPEDGG	ELDS DCK VV	KPGLTQTSVP KPGTTQTSVP	GIV FAAGD WQ D	KK
		310	320	130	340	350	380
Translation of ATTHIREDB Translation of TR	YROALTA YROALTA	AGT GCMAALD AGT GCMAALD	AEHYLQEIGS AEHYLQEIGS	OGKSD OGKSD			

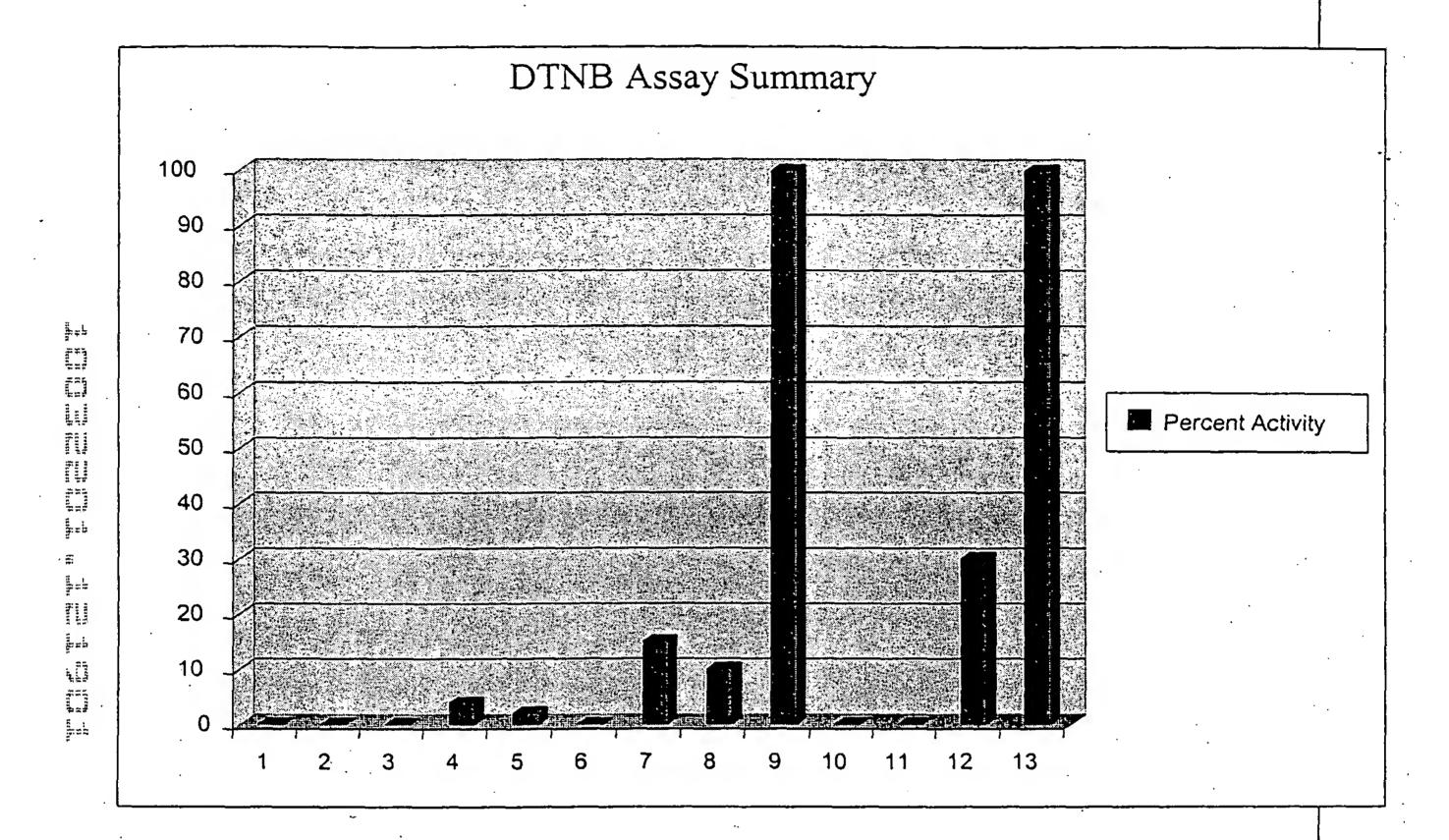


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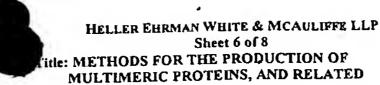
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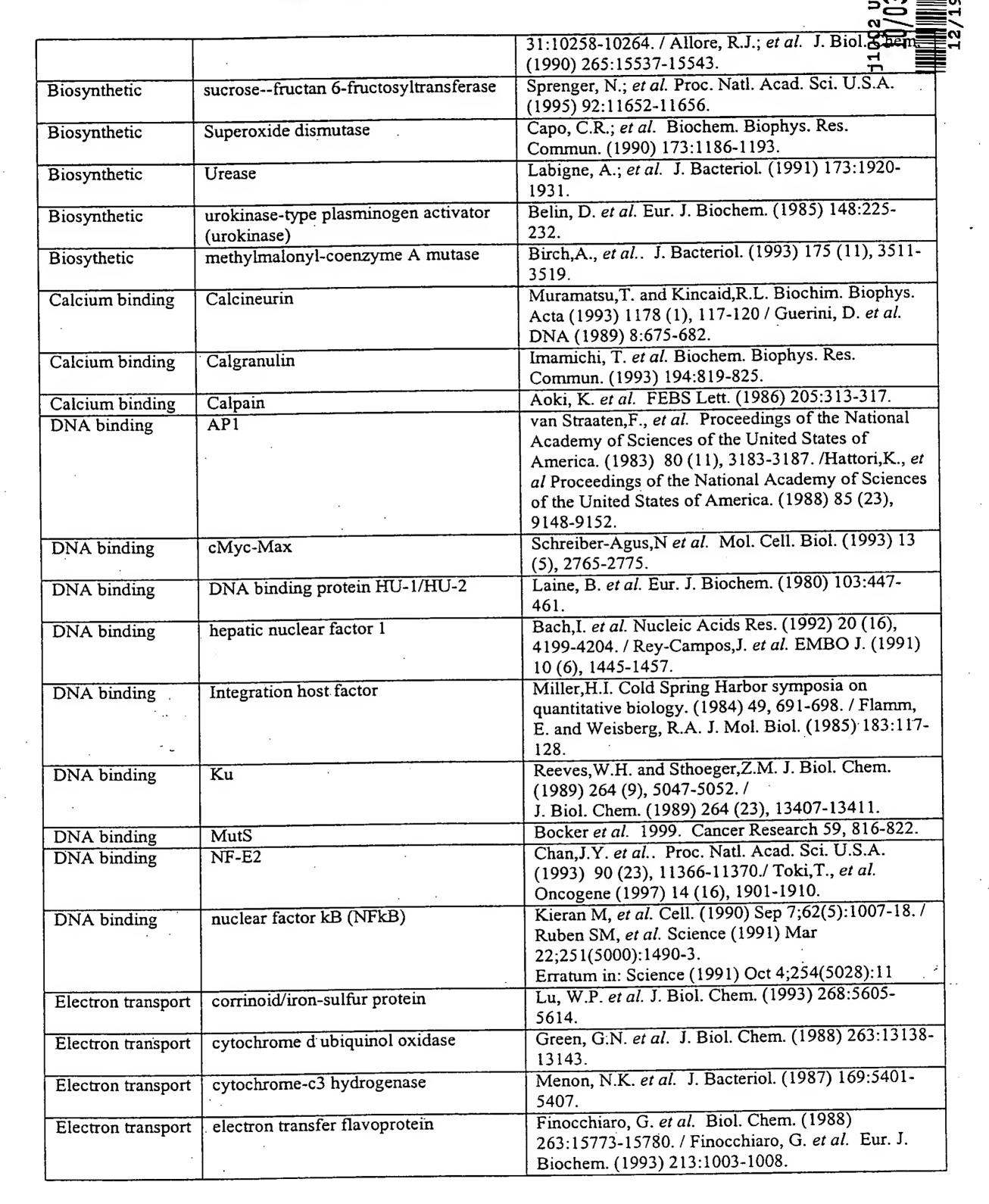
HETEROMULTIMERS

Class	Uataramultimar	Example sequence reference for
Class	Heteromultimer	heteromultimeric subunits
D:4141	3-methyl-2-oxobutanoate	McKean, et al. Biochim. Biophys. Acta (1992)
Biosynthetic	dehydrogenase (2-oxoisovalerate	1171:109-112 / Chuang, J.L., et al FEBS Lett. a
	dehydrogenase (lipoamide))— E1	(1990) 262 (2), 305-309.
	component)	
Biosynthetic 3-oxoadipate CoA-transferase		Parales, R.E. and Harwood, S.C. J. Bacteriol. (1992)
.		174:4657-4666
Biosynthetic	anthranilate synthase:indole-3-glycerol	Zalkin, H.; et al. J. Biol. Chem. (1984) 259:3985-
-	phosphate synthase	3992.
Biosynthetic	beta-ketoacyl-[acyl carrier protein]	Siggaard-Andersen, M. et al. Proc. Natl. Acad. Sci.
•	synthase I	U.S.A. (1991) 88:4114-4118
Biosynthetic	butyrateacetoacetate CoA-transferase	Fischer, R.J., et al. J. Bacteriol. (1993) 175 (21),
	la de la constante	6959-6969. Mutzel, R et al. Proc. Natl. Acad. Sci. U.S.A. (1987)
Biosynthetic	cAMP dependent protein kinase	84:6-10./ Burki, E., et al. Gene (1991) 102 (1), 57-
	, and the second	65.
T	anhamaul phochata comthaga	Shigenobu, S., et al. Nature. (2000) 407 (6800), 81-
Biosynthetic	carbamoyl-phosphate synthase	86.
Diagrama	Creatine kinase	Billadello, J.J.; et al. Biochem. Biophys. Res.
Biosynthetic	Cleatine kinase	Commun. (1986) 138:392-398. / Roman, D.; et al.
		Proc. Natl. Acad. Sci. U.S.A. (1985) 82:8394-8398.
Diographatic	gamma-glutamyltransferase (gamma-	Papandrikopoulou, A.; et al. Eur. J. Biochem.
Biosynthetic	glutamyl transpeptidase)	(1989) 183:693-698.
Biosynthetic	glutathione transferase	Morrow, C.S. et al. Gene (1989) 75:3-11
Biosynthetic	glycerol-3-phosphate dehydrogenase	Cole, S.T. et al. J. Bacteriol. (1988) 170:2448-2456.
Biosynthetic	guanylate cyclase	Hinsch, K.D. et al. FEBS Lett. (1988) 239:29-34/
Diosynthetic	guanylate cyclase	Koesling, D. et al. FEBS Lett. (1990) 266:128-132.
Biosynthetic	heterodisulfide reductase	Smith, D.R., et al. J. Bacteriol. (1997) 179 (22),
Biodynaiono		7135-7155.
Biosynthetic	human cathepsin	Ritonja, A. et al. FEBS Lett. (1988) 228:341-345.
Biosynthetic	Hydrogenase	Menon, N.K. et al. J. Bacteriol. (1990) 172:1969-
		1977.
Biosynthetic	Meprin A	Johnson, G.D. and Hersh, L.B. J. Biol. Chem.
		(1992) 267:13505-13512.
Biosynthetic	methionine adenosyltransferase	Horikawa, S.; Tsukada, K. FEBS Lett. (1992)
		312:37-41.
Biosynthetic	methylmalonyl-CoA mutase	Jackson, C.A. et al. Gene (1995) 167:127-132.
Biosynthetic	mitochondrial processing peptidase	Pollock, R.A. et al. EMBO J. (1988) 7:3493-3500.
Biosynthetic	Na+/K+-exchanging ATPase	Shull, G.E., et al. Biochemistry (1986) 25 (25),
		8125-8132./Mercer,R.W., et al.
		Mol. Cell. Biol. (1986) 6 (11), 3884-3890./
		Mercer, R.W., et al. J. Cell Biol. (1993) 121 (3),
		Cupp, J.R. and McAlister-Henn, L. J. Biol. Chem.
Biosynthetic	NAD(+)-dependent isocitrate	(1992) 267:16417-16423. /Cupp, J.R. and
	dehydrogenase	McAlister-Henn, L.
		J. Biol. Chem. (1991) 266:22199-22205.
B: 11 ::	- Lambarila and farmulal voine midine	Ebbole, D.J.; Zalkin, H. J. Biol. Chem. (1987)
Biosynthetic	phosphoribosylformylglycinamidine	262:8274-8287.
Diameter	synthase protocatechuate 3,4-dioxygenase	Frazee, R.W.; et al. J. Bacteriol. (1993) 175:6194-
Biosynthetic	protocatechuate 3,4-uloxygenase	6202.
Dicambatic	S-100 protein	Engelkamp, D.; et al. Biochemistry (1992)
Biosynthetic	5-100 protein	1 0 1, - ,



COMPOSITIONS
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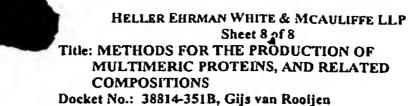


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Electron transport	xylene monooxygenase	Shaw, J.P. and Harayama, S. Eur. J. Biochem.
Zioonon Rumopori		(1992) 209:51-61. / Kasai, Y., et al. J. Bacteriol.
		(2001) 183 (22), 6662-6666.
Growth factor	hepatocyte growth factor	Nakamura, T. et al. Nature (1989) 342:440-443.
Growth factor	human chorionic gonadotropin	Morgan, F.J. et al. J. Biol. Chem. (1975) 250 (13), 5247-5258.
Growth factor	Platelet-derived growth factor	Takimoto, Y., et al. Hiroshima J. Med. Sci. (1993)
		42 (1), 47-52./ Josephs, S.F., et al. Science (1984) 225 (4662), 636-639.
Hormone	Bombyxin	Adachi, T. et al. J. Biol. Chem. (1989) 264:7681-7685.
Hormone	Follicle stimulating hormone	Fiddes, J.C. and Goodman, H.M. J. Mol. Appl. Genet. (1981) 1 (1), 3-18. / Watkins, P.C., et al. DNA (1987) 6 (3), 205-212.
Hormone	Insulin	Bell,G.I., Pictet,R.L., Rutter,W.J., Cordell,B., Tischer,E. and Goodman,H.M. Sequence of the human insulin gene. Nature. 284 (5751), 26-32 (1980)
Hormone	Luteinizing Hormone	Fiddes, J.C. and Goodman, H.M. J. Mol. Appl.
		Genet. (1981) 1 (1), 3-18. / Shome, B. and Parlow, A.F. J. Clin. Endocrinol. Metab. (1973) 36 (3), 618-621.
T.C. man and	Thyroid stimulating hormone	Fiddes, J.C. and Goodman, H.M. J. Mol. Appl.
Hormone	I hyroid stimulating normone	Genet. (1981) 1 (1), 3-18. / Hayashizaki Y, et al. FEBS Lett. (1985) 188 (2), 394-400.
Immune	B-cell antigen receptor complex	Hashimoto, S. et al. J. Immunol. (1993) 150 (2), 491-
		498. / Flaswinkel, H. and Reth, M.
		Immunogenetics (1992) 36 (4), 266-269.
Immune	Cell surface CD8 molecules	Ureta-Vidal, A., et al. Immunogenetics (1999) 49 (7-8), 718-721.
Immune	human complement subcomponent C1q	Sellar, G.C. et al. Biochem. J. (1991) 274:481-490.
Immune	T cell receptor	Talken, B.L. et al. Scand. J. Immunol. (2001) 54 (1-2), 204-210.
Photosynthesis -	C-phycocyanin	Offner, G.D. et al. J. Biol. Chem. (1981) 256:12167-12175. / Troxler, R.F. et al. J. Biol. Chem. (1981) 256:12176-12184.
Photosynthesis	ferroredoxin-thioredoxin reductase	Chow, L.P. et al. Eur. J. Biochem. (1995) 231:149- 156. / Iwadate, H. et al. Eur. J. Biochem. (1994) 223:465-471.
Photosynthesis	Light harvesting complex I	Proc. Natl. Acad. Sci. U.S.A. (1984) 81, 189-192.
Photosynthetic	cytochrome b559	Carrillo, N. et al. Curr Genet. 1986;10(8):619-24.
Protease	ATP-dependent Clp protease	Gerth, U. et al. Gene (1996) 181:77-83. / Kunst,F. et al. Nature (1997) 390 (6657), 249-256.
Receptor	alpha-2-macroglobulin receptor	Strickland, D.K. et al. J. Biol. Chem. (1990) 265:17401-17404. / Strickland, D.K. et al. J. Biol. Chem. (1991) 266:13364-13369.
Receptor	Interleukin-2 receptor	Ishida, N. et al. Nucleic Acids Res. (1985) 13:7579-7589. / Hatakeyama, M. et al. Science (1989) 244:551-556 / Takeshita, T. et al. Science (1992) 257:379-382.
Receptor	platelet-derived growth factor receptor	Lee, K.H. et al. Mol. Cell. Biol. (1990) 10:2237-2246. / Herren, B. et al. Biochim. Biophys. Acta 1173 (3), 294-302 (1993).
Structural	Hemoglobin	Heindell, H.C. et al. Cell (1978) 15 (1), 43-54.



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		Best, J.S. et al. Hoppe-Seyler's Z. Physiol. Chem. (1989) 350 (5), 563-580. / Hardison, R.C. J. Biol. Chem. (1981) 256 (22), 11780-11786.
Structural	human platelet glycoprotein Ib	Wenger, R.H. et al. Biochem. Biophys. Res. Commun. (1988) 156 (1), 389-395. / Yagi, M. et al. J. Biol. Chem. (1994) 269 (26), 17424-17427.
Structural	Plasma fibronectin	Kornblihtt, A.R. et al. Proc. Natl. Acad. Sci. U.S.A. (1983) 80:3218-3222.
Structural	Spectrin	Sahr, K.E. et al. J. Biol. Chem. (1990) 265:4434-4443. / Winkelmann, J.C. et al. J. Biol. Chem. (1990) 265:11827-11832.
Structural	Tubulin	Ponstingl, H. et al. Proc. Natl. Acad. Sci. U.S.A. (1981) 78:2757-2761. / Krauhs, E. et al. Proc. Natl. Acad. Sci. U.S.A. (1981) 78:4156-4160.
Toxin	Agkisacutacin	Cheng, X. et al. Biochem. Biophys. Res. Commun. (1999) 265 (2), 530-535.
Toxin	Beta bungarotoxins	Kondo, K. et al. J. Biochem. (1978) 83:101-115.
Toxin	Crotoxin	Bouchier, C. et al. Nucleic Acids Res. (1988) 16 (18), 9050.
Toxin	Mojave toxin	John, T.R. et al. Gene (1994) 139:229-234.
Toxin	venom protein C9S3	Rowan, E.G. et al. Nucleic Acids Res. (1990) 18:1639. / Joubert, F.J. and Viljoen, C.C. Hoppe- Seyler's Z. Physiol. Chem. (1979) 360:1075-1090.
Miscellaneous	Inhibin	Forage, R.G. et al. Proc. Natl. Acad. Sci. U.S.A. (1986) 83:3091-3095.
Miscellaneous	Monellin	Frank, G. and Zuber, H. Hoppe-Seyler's Z. Physiol. Chem. (1976) 357:585-592.
Miscellaneous	mRNA capping enzyme	Niles, E.G. et al., J. Virology (1986) 153:96-112.
Miscellaneous	Soybean insulin-binding protein si30	Barbashov, S.F. et al. Bioorg. Khim. (1991) 17:421-

423.